containing donor CDRs grafted into an acceptor framework and containing one or more amino acid changes within the framework regions and one or more amino acid changes within the CDRs will have amino acids residues at the changed framework region positions different than the residues at the comparable positions in the acceptor framework. Similarly, such an altered variable region will have amino acid residues at the changed CDR positions different than the residues at the comparable positions in the donor CDRs.

As used herein, the term "nucleic acid" or "nucleic acids" is intended to mean a single- or double-stranded DNA or RNA molecule. A nucleic acid molecule of the invention can be of linear, circular or branched configuration, and can represent either the sense or antisense strand, or both, of a native nucleic acid molecule. The term also is intended to include nucleic acid molecules of both synthetic and natural origin. A nucleic acid molecule of natural origin can be derived from any animal, such as a human, non-human primate, mouse, rat, rabbit, bovine, porcine, ovine, canine, feline, or amphibian, or from a lower eukaryote, such as Drosophila, C. elegans or yeast. A synthetic nucleic acid includes, for example, chemical and enzymatic synthesis. The term "nucleic acid" or "nucleic acids" is similarly intended to include analogues of natural nucleotides which have similar functional properties as the referenced nucleic acid and which can be utilized in a manner similar to naturally occurring nucleotides and nucleosides.

As used herein, the term "coexpressing" is intended to mean the expression of two or more molecules by the same cell. The coexpressed molecules can be

polypeptides or encoding nucleic acids. The coexpression can be, for example, constitutive or inducible. Such nucleic acid sequences can also be expressed simultaneously or, alternatively, regulated independently. Various combinations of these modes of coexpression can additionally be used depending on the number and intended use of the variable region encoding nucleic acids. The term is intended to include the coexpression of members originating from different populations in the same cell. For example, populations of molecules can be coexpressed where single or multiple different species from two or more populations are expressed in the same cell. A specific example includes the coexpression of heavy and light chain variable region populations where at least one member from each population is expressed together in the same cell to produce a library of cells coexpressing different species of heteromers variable region binding fragments. Populations which can be coexpressed can be as small as 2 different species within each population. Additionally, the number of molecules coexpressed from different populations also can be as large as 10^8 or greater, such as in the case where multiple amino acid position changes of multiple framework regions or CDRs in both heavy and light chain antibody variable region populations are produced and coexpressed. Numerous different sized populations of encoding nucleic acids inbetween the the above ranges and greater can also be coexpressed. Those skilled in the art know, or can determine, what modes of coexpression can be used to achieve a particular goal or satisfy a desired need.

As used herein, the term "identifying" is intended to mean detecting by a qualitative or quantitative means, a variable region or altered variable

of the invention by functional or biochemical properties, including, for example, binding affinity of catalytic activity.

As used herein the term "binding affinity" is intended to mean the strength of a binding interaction and therefore includes both the actual binding affinity as well as the apparent binding affinity. The actual binding affinity is a ratio of the association rate over the disassociation rate. Therefore, conferring or optimizing binding affinity includes altering either or both of these components to achieve the desired level of binding affinity. The apparent affinity can include, for example, the avidity of the interaction. For example, a bivalent heteromeric variable region binding fragment can exhibit altered or optimized binding affinity due to its valency.

As used herein, the term "optimizing" when used in reference to a variable region or a functional fragment thereof is intended to mean that the binding affinity of the variable region has been modified compared to the binding affinity of a parent variable region or a donor variable region. A variable region exhibiting optimized activity can exhibit, for example, higher affinity or lower affinity binding, or increased or decreased association or dissociation rates compared to an unaltered variable region. A variable region exhibiting optimized activity also can exhibit increased stability such as increased half-life in a particular organism. For example, an antibody activity can be optimized to increase stability by decreasing susceptibility to proteolysis. An antibody exhibiting optimized activity also can exhibit lower affinity binding, including decreased association rates or